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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/508,516	06/08/00	BEBBINGTON C	078883/0119

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EXAMINER	
WILSON, M	
ART UNIT	PAPER NUMBER
1633	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/508,516	Applicant(s) BEBBINGTON ET AL.	
	Examiner Michael Wilson	Art Unit 1633	

-- The MAILING DATE of this communication appears on th cov r sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 28-45* is/are pending in the application.

4a) Of the above claim(s) *29 and 31-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,28,30 and 42-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Michael C. Wilson.

Applicant's arguments filed 6-25-01, paper number 15, have been fully considered but they are not persuasive. Claim 27 was canceled in the response filed 3-24-00, paper number 6. Claims 43-45 have been added in the response filed 6-25-01. Thus, claims 1-26 and 28-45 are pending.

This application contains claims 29 and 31-41 drawn to an invention nonelected with traverse in Paper No. 12 filed 11-13-00. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-26, 28, 30 and 42-45 are under consideration in the instant office action as they relate to the elected subject matter which is a retroviral vector. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

1. Claims 1-26, 28, 30 and 42 remain rejected and claims 43-45 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for the selective expression of the hygromycin - neomycin gene pair or the hygromycin-p450 gene pair does not reasonably provide enablement for any nucleotide sequence of interest (NOI) as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to use the invention commensurate in scope with these claims for reasons of record.

Applicants invention is directed toward a retroviral vector which yields an activated splice donor/acceptor upon transduction. The translocation of the splice donor site to the 5' of the splice acceptor site is achieved by reverse transcription of a parent vector. Insertion into the host cell's genome of the reverse transcribed DNA originating from the parent vector results in a provirus which has a functional intron. This intron may contain a nucleotide sequence of interest (NOI; page 1, line 10). Since the gene of interest is within the intron, no protein from the gene will be expressed due to splicing out of the sequence in mRNAs transcribed from the provirus. Further, expression of a second gene of interest (second NOI) downstream of the splice acceptor site is activated because of the functioning intron.

The construction of retroviral vectors for the selective expression of foreign genes is unpredictable (Jolly, 1994, Cancer Gene Therapy, Vol. 1(1), page 53). Although the applicants of the instant application have suggested a number of genes which might be used in there vector, they have supplied working examples for two pairs of NOI's (hygromycin/ neomycin and hygromycin/cytochrome p450). Particularly relevant to the design of the vectors described herein is the potential of cryptic splice donor/acceptor sites arising in NOIs and the amount of experimentation required to design vectors which are free of such sites

The presence of cryptic splice sites becoming activated in retroviral transcripts in transduced cells has been well established. Nucleic acid sequences encoding proteins of interest

may comprise unknown splice sites which may become active and prevent expression of the protein (McIvor, 1990, Virology 176:652-55; page 653 first paragraph; Zaboikin, 1998, Human Gene Therapy, 9:2263-2275, see Abstract; Sorrentino, 1995, Blood 15, 86(2):491-501). Specifically, the vector encoding CAT operatively linked to the SV40 promoter taught by applicants was determined after the filing date to contain a cryptic splice site and prevent CAT expression (Ismail, 2000, J. Virol., Vol. 74(5):2365-2371; page 2369). Thus, the conditions required to obtain expression of a gene of interest were unpredictable because of cryptic splice sites within the nucleic acid sequence of interest.

Applicants have provided examples of vectors encoding hygromycin and neomycin or hygromycin and cytochrome p450 that provide expression of said proteins. Thus, in view of the unpredictability in the art at the time of filing, applicants have only enabled one of skill to obtain expression of hygromycin and neomycin or hygromycin and cytochrome p450 and do not enable expressing any NOI as broadly claimed.

Applicants argue that cryptic splice sites would not hinder application of the claimed invention to other NOI. Applicants argue that one of skill would be able to compensate for cryptic splice sites by identifying and altering the sites which is taught in Ismail (2000). Applicants argument is not persuasive because the specification and the art at the time of filing did not teach how to identify and change cryptic splice sites and because Ismail was not available at the time of filing. It was unpredictable whether a gene contained a cryptic splice site. The specification does not overcome the unpredictability in the art by teaching how to sequence and

identify an undesired splice site. Nor does the specification teach how to analyze a transcript to determine the location of the splice site (page 13, line 9, of applicants arguments). The NOI are not limited to cDNA (page 13, line 12, of applicants arguments) or nucleic acid sequences encoding a protein. The splice acceptors are not limited to "strong" splice acceptors (page 13, line 14, of applicants arguments).

The specification does not enable transfecting cells within a host or using the vector claimed for therapy for reasons of record. The specification contemplates transfecting cells *in vivo* and using the vector claimed to treat disease (para. bridging pages 50-51). Claim 20 encompasses a target site that is a cell *in vivo*. Claim 26 is drawn to a vector for use in medicine. Claim 25 and 44 encompass cells within a host that are transfected with the retroviral vector. Claims 28 and 45 encompass a method of transfecting cells *in vivo*.

The state of the art at the time of filing was that specific combination of vector, protein of interest, level of expression and target tissue required to obtain the desired effect *in vivo* using gene therapy was unpredictable (Verma page 239, col. 1; Patterson, 2000, page 2, 2nd full paragraph; Eck, 1996, pages 81- 82).

The specification teaches a number of examples for the construction of gene transfer vectors but does not provide adequate guidance regarding how to use the vectors to obtain the desired therapeutic effect by teaching the level of expression or target tissue required to obtain such an effect. The specification does not provide any working example of a therapeutic retroviral vector or correlate the vectors made to vectors known in the art that provide a

therapeutic effect. Without such guidance, the specification does not overcome the unpredictability in the art at the time of invention. It would have required one of skill in the art at the time the invention was made undue experimentation to determine the route of administration, dosage, level of expression, and target tissue required to use the claimed vector to transfect cells *in vivo* or obtain a therapeutic effect as encompassed by the claims.

Applicants argue that the MLV backbone of the instant invention was used for gene delivery *in vivo* at the time of filing (page 13 of applicants arguments). Applicants argument is not persuasive because the claimed invention is not limited to the MLV vector taught by Jolly and because the vector claimed is not limited to expressing adenosine deaminase. The MLV backbone and the vector claimed are structurally different. As stated above, it was unpredictable what vector could provide adequate expression of a protein of interest. Applicants have not provided adequate correlative evidence that the MLV backbone and the vector claimed would have the same therapeutic effect by teaching that the amount of expression is equivalent *in vivo* or that the vectors target the same tissue. Therefore, the teachings of the MLV backbone do not enable the claimed invention. While Verma states lentiviral vectors provide expression of proteins, the expression did not provide any therapeutic effect. Taken as a whole, Verma taught that the parameters required to obtain a therapeutic effect using gene therapy were not predictable. Therefore, the specification does not enable therapeutic embodiments.

2. Claims 1-26, 28, 30 and 42 remain rejected and claims 43-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 remains indefinite for reasons of record because the phrase "A retroviral vector comprising a functional splice donor site and a functional splice acceptor site" is unclear as it relates to the phrases "wherein the retroviral vector is formed as a result of reverse transcription of a retroviral pro-vector... ... is formed as a result of reverse transcription of the retroviral pro-vector." It cannot be determined how the "retroviral vector" correlates to the "retroviral pro-viral vector" or how the reverse transcription of the "retroviral pro-viral vector" effects the structure or function of the retroviral vector. Claims 2-26, 28, 30 and 42-45 are included because they depend upon claim 1. Applicants arguments do not address this rejection.

Claim 1 as newly amended is indefinite because nucleic acid sequences do not "encode" splice sites - they encode proteins. Splice sites are non-coding regions and do not encode anything. Therefore, the phraseology is incorrect. a) could be "a functional splice donor site" or "a nucleic acid sequence comprising a functional splice donor site."

Claims 4, 7, 8, 11 and 12 remain indefinite because it is unclear how limitations describing the retroviral pro-virus limit the retroviral vector of claim 1. Applicants argue the amendments to the claims make the claims definite. Applicants argument is not persuasive because it remains unclear how the "retroviral vector" correlates to the "retroviral pro-viral vector" or how the

reverse transcription of the "retroviral pro-viral vector" effects the structure or function of the retroviral vector.

Claims 28 and 45 are indefinite because the body of the claims are not commensurate in scope with the preamble of the claims and because the claims do not include essential steps. Obtaining detectable expression of a protein encoded by the vector is considered essential to the claimed method because it is the sole disclosed use for delivering a gene to a cell. Expression of the gene requires more than mere transfection or transduction of a cell with a retroviral vector or particle. Therefore, the claim as written does not include the essential step of obtaining detectable levels of expression of a protein. For example, "a method of transfecting or transducing a cell comprising transfecting or transducing a cell with the retroviral vector of claim 1 such that said protein is expressed to detectable levels" could be acceptable; however, such an amendment would require that the vector comprises a nucleic acid sequence encoding a protein operably linked to a promoter. Claim 1 does not require the vector encodes a protein. Therefore, claim 1 would have to be amended such that the NOI was "a nucleic acid sequence encoding a protein operably linked to a promoter." Applicants disagree with the grounds of rejection but does not provide any arguments. Applicants state the amendment to the claims clarifies the claims. Applicants argument is not persuasive for reasons cited above.

Claim Rejections - 35 USC § 102

3. Claims 1-6, 9, 10, 12-14, 18-25 remain rejected and claims 43 and 44 are rejected under 35 USC 102(b) as being anticipated by Morgenstern (Morgenstern et al., 1990, Nucleic Acids Research 18(12):3587-96) for reasons of record.

Morgenstern described a retroviral vector (prZNSV(X)) comprising a functional splice donor site and functional splice acceptor site. The vectors contained "gag" and "neo," "hygro" or "puro" which are two "NOIs" as claimed. Any nucleic acid sequence that does not function as a splice site and upstream of the splice acceptor is equivalent to the "third NS" in claim 2 that "encodes a non-functional splice donor site" as claimed. Neomycin is considered a "therapeutic agent" or "diagnostic agent" as in claim 5 and an "agent conferring selectablity" as in claim 6. The splice donor site in prZNSV(X) is equivalent to a viral nucleotide sequence that is an intron or part thereof (claims 9 and 10) because it is part of an intronic sequence of viral origin. The retrovirus was packaged into infectious particles (page 3589, legend of Figure 2); therefore, the retrovirus of Morgenstern contains a packaging signal (claim 12). The neo gene is expressed in cells which is equivalent to being "expressed at a primary target site (claim 13). The hygromycin gene of prZNSV(X) can be spliced out and can restrict expression of gag and is, therefore, considered a functional intron that restricts expression of gag (claims 18 and 19). prZNSV(X) was used to infect tissue culture cells (claim 20). The source of prZNSV(X) is the murine oncoretrovirus Moloney murine leukemia virus (MMLV) (claims 21 and 22). The retrovirus of Morgenstern is integrated (claim 23) because the retrovirus is isolated from stable producer cell

lines (para. bridging pages 3588-89) which does not occur without integration. Virus was obtained from packaging lines (page 3588, col. 1, line 11) which is equivalent to obtaining retroviral particles (claim 24). Tissue culture cells were infected with retroviral particles which is equivalent to transducing or transfecting target cells (claims 25 and 44) (page 3588, col. 1, line 18). The phrase "for use in medicine" (claim 43) is an intended use and does not bear patentable weight in considering the art.

Applicants argue that Morgenstern does not anticipate the claimed invention because it teaches splice site inactivation by point mutation. Not all of the vectors of Morgenstern have the point mutation. Furthermore, the claims do not appear to exclude a splice site inactivated by a point mutation. The vector of Morgenstern is not distinguishable over the claims. The amendments to the claims do not distinguish the claims from the vector of Morgenstern.

4. Claims 1 and 15-17 remain rejected under 35 USC 102(b) as being anticipated by Takeda (Takeda et al., 1985, Nature, Vol. 314, 452-454) for reasons of record. Claim 1 was obviously omitted from the heading of the rejection because claim 1 was discussed in the body of the rejection and because claims 15-17 are dependent upon claim 1.

Takeda taught a retroviral vector comprising a nucleic acid sequence encoding heavy chain variable –diversity joining and constant region genes of an immunoglobulin (page 453, figure 1 and figure 1 legend). Several splice donor/acceptor pairs are present which flank nucleotide sequences of interest.

Applicants argue Takeda does not disclose the retroviral vector of the claimed invention. Applicants argument is not persuasive. Applicants have not pointed to one specific difference between the vector of Takeda and the vector claimed. Therefore, the claims remain rejected for reasons of record because Takeda teaches all the elements of the claims.

5. Claims 1 and 9-11 remain rejected under 35 USC 102(b) as being anticipated by Kriegler (Kriegler et al., 1984, Cell, Vol. 38, pages 483-491). Claim 1 was obviously omitted from the heading of the rejection because claim 1 was discussed in the body of the rejection and because claims 9-11 are dependent upon claim 1.

Kriegler taught retroviral vectors containing several splice donors/acceptors and the early genes of SV40 (page 484, Figure 1) which includes the small t antigen as claimed.

Applicants argue Kriegler does not disclose the retroviral vector of the claimed invention. Applicants argument is not persuasive. Applicants have not pointed to one specific difference between the vector of Kriegler and the vector claimed. Therefore, the claims remain rejected for reasons of record because Kriegler taught all the elements of the claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

Deborah Clark

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